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EXAMINER	
REDDIG, PETER J	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/668,724	SRIVASTAVA ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,80-82,85,91-104,107,110,111,115 and 121* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,80-82,85,91-104,107,110,111,115 and 121* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/21/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed March 21, 2007 in response to the Office Action of September 21, 2006 is acknowledged and has been entered. Claims 31, 80-82, 85, 91-104,107, 110, 111, 115, and 121 are currently being examined.

Declaration of Dr. Rammensee

2. The declaration under 37 CFR 1.132 filed March 21, 2007 is insufficient to overcome the rejection of claims 31, 80-82, 85, 91-104,107, 110,111, 115, and 121 based upon lack of enablement as set forth in the Office Action of September 21, 2006 action and for the reasons set forth below.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 31, 80-82, 85, 91-104,107, 110,111, 115, and 121 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons previously set forth in the Office Action of September 21, 2006 on pages 2-7 and in the Office Action of February 8, 2006 pages 4-8.

Enablement of "an α2M receptor fragment"

4. Applicant argues that in their Amendment filed May 8, 2006, Applicants maintained that the specification was enabling for the use of "an α2M receptor fragment" according to the claimed methods because (i) the structure of the α2M receptor is known in the art; (ii) the specification provides a specific example of a fragment having the desired activity, i.e., the ability to interfere with the interaction of a heat shock protein with the α2M receptor, i.e., the p80 fragment, which can be used as a positive control and/or as a starting point for identifying subfragments of p80 which retain the desired activity; (iii) the specification provides the amino acid sequence structure of other exemplary fragments of the α2M receptor that can be tested for the desired activity; and (iv) assays are described by the specification and known in the art which

can be used to distinguish those fragments having the desired activity from those that do not (e.g., receptor binding assays and antigen re-presentation assays).

Applicants argue that the Examiner provides no explanation as to why the teachings in Applicants' specification combined with the knowledge in the art (i. e., the known structure of the α2M receptor, the structure of exemplary α2M receptor fragments, including one, the p80 fragment, demonstrated by Applicants' specification to have the activity recited in the claims (i.e., the ability to interfere with the interaction of a heat shock protein with the α2M receptor), and routine assays for determining whether a fragment interferes with the interaction of a heat shock protein with the α2M receptor) would not provide the skilled practitioner with the ability to make and use fragments of the α2M receptor, in addition to the p80 fragment exemplified in the specification, according to the claimed methods and without undue experimentation. Applicants respectfully remind the Examiner that the specification must be taken as in compliance with the enablement requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Brana, 51 F.3d 1560, 1566 (Fed. Cir. 1995) (emphasis in original). Thus, the burden is on the Examiner to provide evidence showing that one of ordinary skill in the art would have some basis to reasonably doubt Applicants' asserted utility on its face. Id. Applicants argue that there is nothing inherently unbelievable or scientifically implausible about their claim that, given the guidance in the specification and the p80 fragment as a starting point, fragments of the α2M receptor having the activity recited in the claims, in addition to the p80 fragment, can be identified by routine testing of the type that is typically done by protein chemists, i.e., the ability to identify the minimal inhibitory fragment(s) of a polypeptide that has demonstrated the ability to interfere with the interaction between a receptor (such as the α2M receptor) and its ligand (such as a heat shock protein). To summarize, Applicants argue that the p80 fragment has the activity recited in the claims (i.e., the ability to interfere with the interaction of a heat shock protein with the α2M receptor) and it is reasonable to expect that one or more subfragments of p80 will retain that activity. All that is required to identify such subfragments is routine experimentation, i.e., testing subfragments of p80 to identify those

having the desired activity using e.g., binding assays and/or re-presentation assays which are both known in the art and taught by the specification.

Applicants argue that the Examiner also relies on Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916 (Fed. Cir. 2004) to support his assertion that the screening assays taught by the specification do not enable the claimed invention because "they are merely a wish or plan for obtaining the claimed chemical invention" (see the Office Action at p. 3, para. 3). Applicants understand the Examiner to be referring to assays to test for the activity recited in the claims, i.e., the ability to interfere with the interaction of a heat shock protein with the α2M receptor (e.g., receptor binding assays and re-presentation assays). In response, Applicants first note that the court in Rochester did not reach the issue of enablement, having decided the case on finding of lack of written description. See Rochester at 930. Applicants argue that nevertheless, the Examiner's contention that the screening assays are "merely a wish or plan for obtaining the claimed chemical invention" cannot be reconciled with the specific teachings in the specification which provide the structure of the α2M receptor and a fragment of the receptor having the activity recited in the claims as well as the structure of additional, exemplary fragments. Thus, unlike the compound required to practice the claimed method in Rochester, which was defined only by its function, here the structure of the α2M receptor, as well as exemplary fragments of the receptor and how to make them, are described by Applicants' specification (see e.g., the specification at p. 54, lines 1-27). In contrast, the specification in Rochester did not describe by structure, formula, chemical name, or physical properties a single example of a cyclooxygenase inhibitor for use in the claimed method. Id. at 927-28 (noting that "it is undisputed that the '850 patent does not disclose any compounds that can be used in the claimed methods"). Accordingly, Applicants submit that the Examiner's reliance on Rochester is misplaced and maintain that the present specification fully enables the claimed methods.

The arguments have been considered, but have not been found persuasive because Applicants are reiterating arguments previously set forth and none of the examples are commensurate in scope with the claimed invention because none of the claims are drawn to a method of inhibiting an immune response in a human comprising administering to a human a polypeptide consisting of the p80 fragment of the α2M receptor, thus the above arguments do

not provide support for the method of claim 31 drawn to using an α2M receptor fragment that interferes with the interaction of a heat shock protein with the α2M receptor to inhibit an immune response in a human . Although the structure of the α2M receptor is known in the art, neither the art nor the specification teach the structure of an α2M receptor fragment effective to inhibit an immune response in a human.

In regard to *Rochester v. Searle* although the written description and enablement rejections have been found to be distinct wherein it can be found that written description is found while enablement is not or that enablement is found, even though the invention is not described, and the analysis of these two provisions is different, considerable overlap has been found in decisions involving written description and enablement. It is noted however, that in the instant case, neither written description nor enablement provisions of 35 USC 112, first paragraph have been found to be satisfied. Further, although the findings in Rochester are drawn to written description and not to enablement, it is clear that written description is in fact critical to the enablement of these claims. Although the fact patterns of the two cases are not identical but are similar in that, although the structure of the α2M receptor and fragments are known, α2M receptor fragments that inhibit an immune response in a human are not known. In point of fact and as repeatedly stressed by Applicant (see above) the making of the claimed receptor fragment for inhibiting an immune response in a human is completely dependent upon screening assays which will identify the uncharacterized structures that will function as claimed. Thus, although not identical in fact pattern, the essential features of the two cases are indeed the same, (1) both cases are drawn to drugs effective for treatment, (2) both cases are drawn to specific structures that have not been described, (3) both cases require that screening assays be used to identify the structures that would be expected to function as claimed. Thus, as drawn to the screening arguments, it is clear that screening, identical to the Rochester, is critical to the claimed invention and for the reasons set forth above, these arguments are not persuasive.

5. Applicants argue that the Examiner further contends that "the specification does not provide the necessary guidance to the practitioner to enable the predictable making of the broadly claimed invention, that is the ability to predictably distinguish between those fragments that will interfere with the interaction of a heat shock protein with the α2M receptor and those

that will not" (see the Office Action at p. 4 para. 1) (emphasis added). Applicants argue that the Examiner provides no explanation as to why the routine assays described in the specification, such as receptor binding assays and re-presentation assays, would not provide the skilled practitioner with the ability to distinguish interfering fragments from non-interfering fragments, especially in view of the correlation between in vitro and in vivo activity discussed below. Applicants argue that there is nothing inherently unbelievable or scientifically implausible about the claim that the skilled practitioner can distinguish interfering from non-interfering fragments using the assays described in the specification or other routine assays known in the art. Applicants refer the Examiner to the discussion of the rule set forth in In re Brana above and submit that the Examiner has failed to meet his burden with respect to establishing a prima facie case of lack of enablement on this basis.

The arguments have been carefully considered but have not been found persuasive because, although Applicants suggest that receptor binding assays and re-presentation assays would provide the skilled practitioner with the ability to distinguish interfering fragments from non-interfering fragments, as previously set forth and above the screening assays taught and exemplified in the specification do not enable the claimed invention because of the precedent set in *Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004 that screening assays are not sufficient to enable an invention as previously set forth and above.

The evidence provided by Applicants shows that compounds that interfere with heat shock protein-α2M receptor interactions in vitro have in vitro activity that correlates with in vivo activity.

7. Applicants argue that Applicants have provided ample evidence that a compound's activity in an in vitro re-presentation assay had been demonstrated to correlate with its in vivo activity, this demonstration being in 1995, well before the filing date of the instant application in 2000 (see the Amendment dated June 9, 2005 ("the 2005 Amendment") at p. 12, last para. to p. 13, first para., and Suto and Srivastava, 1995, Science 269:1585-88 ("Suto 1995" Ref. No. "CL" of Applicants' Information Disclosure Statement)). Applicants also direct the Examiner's attention to a declaration of Dr. Hans-Georg Rammensee, Ph.D ("Declaration") submitted herewith, in support of this position. Applicants argue that in the Declaration, Dr. Rammensee, citing Suto 1995, states that it was known in the art at June 2000 that mammalian heat shock

proteins can elicit an antigen-specific immune response against peptide complexed to the heat shock protein and that this immune response is characterized by a peptide-specific activation of T cells, which was measured either in vitro as a specific T cell response against the peptide (i.e., re\-presentation assay), or in vivo as protective immunity against transplanted tumor cells in the mouse tumor transplantation model (see Declaration at ¶ 8). Applicants submit that these established in vitro and in vivo assays to measure specific T cell response can also be applied to assay the ability of compounds that interfere with the interaction of the α2M receptor and a heat shock protein to inhibit an antigen-specific immune response elicited by the heat shock protein, as demonstrated in the present specification.

The arguments have been considered, but have not been found persuasive because Applicants are reiterating arguments previously set forth and rejected for the reasons of record and the teachings of Suto and Srivastava, 1995 and Abbas et al. 1991, cited in the Declaration at ¶ 8, are not drawn to methods of using α2M receptor fragments or α2M fragment for inhibiting an immune response and are commensurate in scope with the claimed invention, thus the above arguments do not provide support for the method of claim 31. Furthermore, screening assays are not sufficient to enable an invention as previously set forth and above.

8. Applicants argue that that the submitted references and the declaration of Dr. Hans-Georg Rammensee, PhD demonstrate a correlation between the ability of a compound to inhibit an immune response in an in vitro re-presentation assay (i. e., an antigen-specific T cell response) and the ability of the compound to inhibit an in vivo immune response. Applicants argue that Binder 2004 shows that the activation of antigen-specific T cells by gp96 complexed peptide is inhibited by α2M and also by another ligand of the α2M receptor, RAP, in an in vitro re\-presentation assay (see Binder 2004 Fig. 2A at p. 6130). Applicants argue that Dr. Rammensee states that this in vitro activity was also demonstrated to correlate with the ability to inhibit antigen-specific T cell activation in vivo (see Declaration at ¶ 13). Applicants argue that mice were immunized with gp96-peptide complexes alone, or in the presence of either α2M or an anti-α2M receptor antibody and antigen presenting cells were then isolated from the draining lymph nodes of the immunized mice. Applicants argue that the results demonstrated that the antigen presenting cells from mice immunized in the presence of either α2M or the antibody

were unable to activate T cells (see Binder 2004 at p. 6130, col. 2 to p. 6131, col. 1, and Fig. 3). Applicants argue that thus, Dr. Rammensee concludes that Binder 2004 shows a correlation between the inhibitory activity of a compound, α2M, in an in vitro re-presentation assay and its ability to inhibit an in vivo immune response (see Declaration at ¶ 13).

Applicants argue that, as explained by Dr. Rammensee indicates, Binder 2004 also demonstrates such a correlation for another substance, polyclonal anti-a2M receptor antibody (also referred to in the literature as "anti-CD91" antibody) (see Declaration at ¶ 12; and the 2004 Amendment at p. 12, last para. to p. 13, para. 1). Specifically, Binder 2004 shows that a polyclonal anti-α2M receptor antibody, a compound shown by Applicants' specification to inhibit an immune response elicited by gp96 in an in vitro re-presentation assay, also inhibits the immune response elicited by gp96 in two different assays of in vivo activity (see Declaration at ¶ 12). The first assay was described above. To summarize, mice were immunized with gp96-peptide complexes either alone or in combination with an anti-α2M receptor antibody (or α2M, as discussed above) (see Binder 2004 Fig. 3B at p. 6131). Cells from the lymph nodes of immunized mice were used for stimulation of antigen-specific T cells. The results in Fig. 3B demonstrate that both the antibody and α2M effectively inhibited the activation of antigen-specific T cells by the gp96-peptide complexes. The second assay was a tumor rejection assay (see Binder 2004 Fig. 5 at p. 6133). In this assay, mice were immunized with gp96-peptide complexes obtained from tumor cells, either alone or in combination with anti-α2M receptor antibody and then injected with tumor cells. (see Binder 2004 at p. 6131, col. 2, para. 3, and Fig. 5 at p. 6133). Mice immunized with gp96 complexes from the cancer cells showed very little tumor growth (see Fig. 5, middle row, left panel). However, this anti-tumor immunity was effectively inhibited by co-administration with the anti-α2M receptor antibody (but not by co-administration of the control antibody) (see Fig. 5, middle row, second and third panels from left). Applicants argue that these data, combined with the teachings of Applicants' specification, demonstrate a correlation between the inhibitory activity of anti-α2M receptor antibodies in an in vitro re-presentation assay, i.e., their ability to inhibit an antigen-specific T cell response in vitro, and their ability to inhibit an immune response in vivo, i.e., to inhibit an antigen-specific T cell activation or to inhibit tumor growth in vivo (see Declaration at ¶ 12).

The arguments have been considered, but have not been found persuasive because Applicants are reiterating arguments previously set forth and rejected for the reasons of record and the teachings of Binder 2004 are not drawn to methods of using α2M receptor fragments or α2M fragment for inhibiting an immune response and are commensurate in scope with the claimed invention and does not teach which, if any, fragments of α2M or the α2M receptor can interfere with a heat shock protein interaction with the α2M receptor in vitro or in vivo, thus the above arguments do not provide support for the method of claim 31. Furthermore, screening assays are not sufficient to enable an invention as previously set forth and above.

9. Applicants argue that the results of Binder 2004 were substantiated by Binder 2002 which demonstrates that a polyclonal anti-α2M receptor antibody inhibits the protective immunity elicited by gp96 in vivo, i.e., in a mouse tumor transplantation model system (see Binder 2002 at p. 19 and Fig. 3; and Declaration at ¶ 12). In the Declaration, Dr. Rammensee discusses the in vivo experiment presented in Binder 2002 where mice were immunized with gp96-peptide complexes plus either the anti-α2M receptor antibody or an isotype control antibody (see Declaration at ¶ 12). Additional antibody was administered at the same site each day for two days after each immunization. Live tumor cells were injected intradermally one week after the last immunization and tumor growth (volume) was measured over a period of about 20 days. As shown in Figure 3, top left panel of Binder 2002, mice immunized with gp96-peptide complexes and the isotype control antibody experienced very little tumor growth. In contrast, mice immunized with gp96-peptide complexes and the anti-α2M receptor antibody showed considerable tumor growth, demonstrating that the antibody blocked the protective immunity of the gp96-peptide complexes (see Figure 3, bottom left panel; and Declaration at ¶ 12).

The arguments have been considered, but have not been found persuasive because Applicants are reiterating arguments previously set forth and are rejected for the reasons of record and Binder 2002 and 2004 teach one example where administration of anti-CD91 antibody inhibited an immune response in a mouse model and are not drawn to methods of using α2M receptor fragments or α2M fragment for inhibiting an immune response and thus are not commensurate in scope with the claimed invention and do not teach which, if any, fragments of α2M or the α2M receptor can interfere with a heat shock protein interaction with the α2M

receptor in vitro or in vivo, thus the above arguments do not provide support for the method of claim 31. Furthermore, screening assays are not sufficient to enable an invention as previously set forth and above.

10. Applicants argue that the results of Binder 2004, 2002 and the specification were substantiated by Basu 2001, which demonstrates that a number of compounds that interfere with the interaction of a heat shock protein with the α2M receptor also inhibit an immune response (i.e., a T cell response) as measured by an in vitro re-presentation assay. In Basu 2001, antigen presenting cells were pulsed with gp96 complexed with antigenic peptide (AH 1/19) in the presence of increasing concentrations of either gp96, hsp90, hsp70, or serum albumin, and T cell activation was measured by cytokine release (see Basu 2001 at p. 305, col. 2, para. 2-3, and Fig. 5A). The results demonstrated a dose-dependent inhibition of T cell activation with increasing concentrations of each of the inhibitors, gp96, hsp90, or hsp70. Basu 2001 further demonstrated that α2M and a monoclonal anti-α2M receptor antibody (two compounds that interfere with the interaction between heat shock protein and the α2M receptor) both effectively blocked re-presentation of the antigenic peptide by each of the heat shock proteins, gp96, hsp90, hspT0, and calreticulin (see Basu 2001 at p. 305, col. 2, para 4, to p. 306, col. 2, para. 1, and Fig. 5B and 5C; and p.312, col. 1 para. 1 (anti-CD91 antibody was clone 5A6 from Progen)). Applicants argue that Dr. Rammensee concludes that Basu 2001 provides a further demonstration that compounds that interfere with the interaction between a heat shock protein and the α2M receptor effectively inhibit an immune response and that gp96, hsp90, hsp70, α2M, and an antibody against the α2M receptor are all effective in this context (see Declaration at ¶ 14).

Although Basu 2001 demonstrated that α2M and a monoclonal anti-α2M receptor antibody both effectively blocked re-presentation of the antigenic peptide by each of the heat shock proteins, gp96, hsp90, hspT0, and calreticulin, the arguments have not been found persuasive because the teachings of Basu 2001 are not drawn to methods of using α2M receptor fragments or α2M fragment for inhibiting an immune response and thus are not commensurate in scope with the claimed invention and do not teach which fragments of α2M or the α2M receptor can interfere with a heat shock protein interaction with the α2M receptor in vitro or in vivo, thus

the above arguments do not provide support for the method of claim 31. Furthermore, screening assays are not sufficient to enable an invention as previously set forth and above.

11. Applicants argue that as explained by Dr. Rammensee, Chandawarkar 2004 provides evidence validating the correlation between the in vitro activity of gp96 to inhibit T cell activation in a re-presentation assay and the in vivo activity of gp96 to block anti-tumor activity in vivo (see Declaration at ¶ 14). In particular, Chandawarkar 2004 demonstrates that high-dose gp96 effectively blocked anti-tumor immunity generated by gp96 (in the form of gp96-peptide complexes2 derived from Meth A fibrosarcoma) in mice (see Chandawarkar 2004 at p. 616, col. 2 to p. 618, col. 1 and Figs. 1 and 2). In Chandawarkar 2004, a high-dose (90 lag) of gp96 derived from Meth A fibrosarcoma or normal liver administered concurrently with an optimal immunizing low-dose (10 μg) of gp96 derived from Meth A fibrosarcoma effectively suppressed tumor immunity of mice challenged with live Meth A cells (see Chandawarkar 2004 at p. 616, col. 1 to p. 617, col. 1 and Fig. 1). Further, this immunosuppressive high-dose of gp96 was only effective when it was administered concurrently with or subsequent to the optimal immunizing low-dose of gp96 derived from Meth A fibrosarcoma (see Chandawarkar 2004 at p. 617, col. 1 to p. 618, col. 1 and Fig. 2). Thus, Dr. Rammensee concludes that the in vivo data in Chandawarkar 2004 combined with the in vitro data in Basu 2001, showing that gp96 inhibited an antigen-specific T cell response in an in vitro re- presentation assay, demonstrate a correlation between the inhibitory activity of gp96 in vitro and its ability to inhibit an immune response in vivo (see Declaration at ¶ 14).

Applicants' arguments have been considered, but have not been found persuasive because the teachings of Chandawarkar 2004 are drawn to immune modulation with high doses of gp96 and are not drawn to methods of using α2M receptor fragments or α2M fragment for inhibiting an immune response and thus are not commensurate in scope with the claimed invention. Furthermore, Chandawarkar 2004 teach that studies in vitro with effects of increasing concentrations of gp96 on antigen presenting cell function do not reveal a critical threshold at which the antigen presenting cells change qualitatively, see para. bridging p. 621-622. Thus, it does not appear that the teachings Chandawarkar 2004 can be predictably be used to extrapolate between the in vitro activity of gp96 to inhibit T cell activation in a re-presentation assay and the

in vivo activity of gp96 to block anti-tumor activity in vivo because antigen presenting cells do not appear to change in response to increasing concentration of gp96, therefore the effect of high levels do not appear to be predicably mediated by the α2M receptor. Thus the in vivo function of high does gp96 does not appear to predictably correlate with its in vitro effect on antigen presenting cells.

12. Applicants argue that in summary, Dr. Rammensee concludes that the data for gp96, α2M, and anti-α2M receptor antibodies, as described in the Declaration, demonstrate a correlation between the in vitro activity and the in vivo activity of compounds that are expected to interfere with the heat shock protein-α2M receptor interaction (see Declaration at ¶ 15). The post-filing evidence of Basu 2001, Binder 2002, Binder 2004, and Chandawarkar 2004 demonstrates a correlation between the in vitro activity and the in vivo activity of three substances that are expected to interfere with a heat shock protein-α2M receptor interaction, gp96, α2M, and anti-α2M receptor antibodies, using established assays (i.e., in vitro re-presentation assay and in vivo mouse tumor transplantation model system) that were taught in the art well before June 2000, as evidenced by Suto 1995 (see Declaration at ¶¶ 8 and 15).

Applicants' arguments have been considered, but have not been found persuasive because, as set forth above, the teachings of Basu 2001, Binder 2002, Binder 2004, and Chandawarkar 2004 are not commensurate in scope with the claimed invention and do not provide teachings of α2M receptor fragments or α2M fragment that can inhibit an immune response. Although the assays of Basu 2001, Binder 2002, Binder 2004, and Chandawarkar 2004 may have been taught in the art before June 2000 screening assays are not sufficient to enable an invention as previously set forth and above.

13. Applicants argue that they understand the Examiner to be requiring that they demonstrate a correlation between in vitro and in vivo activity for each of the compounds recited in the claims, i.e., for an α2M receptor fragment and an α2M fragment, as well as for an α2M receptor antibody. In response, Applicants argue that such a requirement is improper because 35 U.S.C. § 112 does not require in vivo testing of every species within a claim, provided there is a reasonable correlation between in vitro results and in vivo activity. Fujikawa v. Wattanasin, 93 F.3d 1559, 1565 (Fed. Cir. 1996). Applicants have shown that a reasonable correlation exists by

demonstrating a correlation for the genus of compounds that interfere with the interaction of a heat shock protein with an α2M receptor. Applicants have demonstrated this by coming forward with both in vitro and in vivo evidence for three examples of such interfering compounds, gp96, α2M, and anti-α2M receptor antibodies.

Applicants argue that in view of the data put forward by Applicants for the genus of compounds that interferes with the interaction of a heat shock protein with an α2M receptor, Applicants maintain that it is reasonable to expect that the compounds recited in the claims, i.e., antibodies and α2M receptor fragments and α2M fragments, would demonstrate a similar correlation between their activity in an in vitro re-presentation assay and their in vivo activity because, like the antibodies, the fragments having in vitro activity will be those that interfere with the interaction between a heat shock protein and the α2M receptor. It is reasonable to expect that a fragment having such interfering activity in vitro will have similar activity in vivo, and thus will inhibit an immune response elicited by the interaction of heat shock protein with the α2M receptor, as was demonstrated for the anti-α2M receptor antibodies, for α2M, and for gp96.

Applicants' arguments have been considered, but have not been found persuasive because Applicants' have not established that in vitro tests of α2M receptor fragments or α2M fragment correlate with inhibiting an immune response in vivo because none of the cited evidence demonstrates a correlation between α2M receptor fragments or α2M fragment in vitro activity and inhibiting an immune response in vivo because, as set forth above, the evidence is not commensurate in scope with the claimed invention. Furthermore, Applicants reliance on Fujikawa v. Wattanasin appears to be insufficient with regard to enablement of in vitro tests because did not reach the issue of enablement, but was deciding the issue of utility of a compound in relation to *in vitro* and *in vivo* tests and not enablement. Furthermore, unlike the Fujikawa v. Wattanasin case where in vitro activity had been observed for the compound for inhibiting cholesterol biosynthesis, no such in vitro activity has been demonstrated for α2M receptor fragments or α2M fragments, thus the fact pattern of the case does not provide support for the instant claims.

14. Applicants argue that the Examiner provides no basis, other than a conclusory statement that the art is unpredictable, for his reasoning that one of skill would doubt that the invention would function as claimed with respect to an α2M fragment that interferes with the interaction of a heat shock protein with the α2M receptor. Applicants have provided evidence that α2M is able to interfere directly with the interaction between a heat shock protein and the α2M receptor, i.e., as measured by a competitive binding assay (see Binder 2004, Fig. 1A) and that α2M inhibits an immune response elicited by heat shock protein (see Applicants' specification at p. 73, lines 20-28; Binder 2004 Figs. 2A and 3B; and Basu 2001 Fig. 5B). Given this data provided by Applicants demonstrating that α2M itself has the activity recited in the claims, Applicants argue that there is nothing inherently unbelievable or scientifically implausible about their position that it is a matter of routine skill to identify one or more fragments of α2M that retain the activity which Applicants have demonstrated for α2M itself. Moreover, Applicants argue that the specification provides sufficient guidance for the genus of α2M fragments with the desired activity by describing twelve representative species and by describing a combination of identifying characteristics of the genus including amino acid sequence structure and functional characteristics that correlate with the sequence structure. For example, the specification provides twelve exemplary α2M fragments, SEQ ID NOS: 8-19, at page 51, lines 16-22. The specification also provides the specific portions of α2M that interact with the α2M receptor, namely amino acids 1314-1451, described at page 13, lines 27-29, Fig. 7B, and in the references provided at page 3, line 34 through page 4, line 7, including Salvesent et al., 1992 FEBS Lett. 313:198-202 and Holtet et al., 1994 FEBS Lett. 344:242-246. Finally, the specification teaches that there is an art-recognized correlation between the structure of the α2M receptor-binding domain identified in Figure 7B as amino acids 1314-1451, and the functional ability of α2M to bind to the α2M receptor. Moreover, at page 4, lines 8-13, the specification provides that an "[a]lignment of α2M receptor ligands identifies a conserved domain" which "spans amino acids 1366-1392 of human α2M' and that two of those conserved residues are required for binding to the α2M receptor, as demonstrated by Nielsen et al., 1996 J. Biol. Chem. 271:12909-12912. Applicants argue that the kind of experimentation required to test whether a particular α2M fragment interferes with the interaction between a heat shock protein and the α2M receptor is of the type routinely

conducted by protein chemists to identify the minimal inhibitory fragment(s) of a polypeptide that has been demonstrated to interfere with the interaction between a receptor and its ligand. Applicants argue that the Examiner also contends that "the specification does not provide the necessary guidance to the practitioner to enable the predictable making of the broadly claimed invention, that is the ability to predictably distinguish between those fragments that will interfere with the interaction of a heat shock protein with the a2M receptor from those that will not" (OA p. 6 para. 1) (emphasis added). Applicants argue that the Examiner provides no explanation regarding why the routine assays described in the specification (e.g., receptor binding assays and re-presentation assays; see the specification at Section 5.2.1, p. 27-32 (receptor-ligand binding assays) and the re-presentation assays described in the specific example at p. 69, lines 27-33) combined with the knowledge in the art would not provide the skilled practitioner with the ability to distinguish interfering fragments from non-interfering fragments.

The arguments have been considered, but have not been found persuasive because Applicants are reiterating arguments previously set forth and none of the examples are commensurate in scope with the claimed invention because the examples are not drawn to methods of using α2M fragment for inhibiting an immune response and thus are not commensurate in scope with the claimed invention and do not teach which fragments of α2 can interfere with a heat shock protein interaction with the α2M receptor and inhibit an immune response in a human and thus do not establish a correlation between the in vitro assays taught in the specification and inhibiting an immune response. Although the screening assays described in the specification may be routine they do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays are not sufficient to enable an invention since they are merely a wish or plan for obtaining the claimed chemical invention, as previously set forth above.

15. Applicants argue that the Examiner also contends that the evidence of a correlation between the in vitro re-presentation assays and an in vivo immune response provided by Applicants is not persuasive "because Binder et al. (2002, 2004, IDS) teach one example where administration of anti-CD91 antibody inhibited an immune response in a mouse model, but did not exemplify inhibition of immune response with any α2M fragments or α2M receptor

fragments" (OA at p. 7, para 2). As with the rejection pertaining to α2M receptor fragments discussed above, Applicants understand the Examiner to be improperly requiring in vivo data in support of each compound recited in the claims. Applicants maintain that they have demonstrated a reasonable correlation between a compound's activity in an in vitro re-presentation assay and its ability to elicit or inhibit an immune response in vivo for the reasons discussed above, and 35 U.S.C. § 112 requires no more. Applicants point out that, as discussed above, they have demonstrated a correlation between the activity of a compound in an in vitro re-presentation assay and its ability to inhibit or elicit an immune response in vivo, not only for anti-α2M receptor antibodies but also for α2M and heat shock proteins.

Applicants' arguments have been considered, but have not been found persuasive because Applicants' have not established that in vitro tests of α2M fragments correlate with inhibiting an immune response in vivo because none of the cited evidence demonstrates a correlation between α2M fragments in vitro activity and inhibiting an immune response in vivo because, as set forth above, the evidence is not commensurate in scope with the claimed invention.

16. Applicants argue that the Examiner does not dispute that Applicants have demonstrated a reasonable correlation between the ability of a compound to modulate an immune response in an in vitro re-presentation assay and its ability to similarly modulate an immune response in vivo. However, the Examiner contends that this evidence is not persuasive because there is "a poor correlation between induction of specific T-cells and the clinical responses" (see the Office Action at p. 7 para. 2, citing Bellone et al., 1999 "Cancer immunotherapy: synthetic and natural peptides in the balance," Immunology Today 20:457-462 ("Bellone")). Applicants understand this rejection to be based on an alleged lack of utility for the claimed method under 35 U.S.C. 101 and 112 (see Rasmusson v. Smithkline BeechamCorp., WL 1501450 at page 3 (Fed. Cir. 2005) ("the how to use prong of section 112 incorporates as a matter of law the requirement of 35 U.S.C. 101 that the specification disclose as a matter of fact a practical utility for the invention."). Applicants argue that Bellone teaches that, although synthetic and natural peptides used as cancer vaccines are often able to elicit an antigen-specific T cell response in vivo, this T cell response does not generally correlate with a clinical response to the tumor in cancer immunotherapy (see Bellone at p. 457, col. 1, last para. and p. 459, col. 1, first para.). First,

Applicants point out that the claims are not directed to a "clinical response" to a tumor, but rather to inhibiting an immune response. Thus, whatever Bellone may suggest about the correlation between the ability of a compound to elicit an in vivo T cell response and its ability to elicit a clinical response to a tumor, Bellone does not call into question the correlation between a compound's activity in an in vitro re-presentation assay and its ability to elicit an in vivo immune response, which is the relevant correlation with respect to the claimed methods. Applicants argue that to the extent that the Examiner's rejection suggests that Applicants must present data of clinical efficacy in humans for the claimed methods of inhibiting an immune response, Applicants further note that it is improper to request such evidence of safety and efficacy in the treatment of humans, when the evidence that has been presented reasonably correlates with the asserted utility, as it does in the instant case. See e.g., In re Brana, 5 1 F.3d 1560, 1567 (Fed. Cir. 1995) (Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings. ")(quoting Scott v. Finney, 34 F.3d 1 05 8, 1063 (Fed. Cir. 1994)). Instead, the court stated that *Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans*. Id. at 1568 (internal citations omitted)(emphasis added). The court further stated that "proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility." Id. at 1567 (quoting In re Krimmel, 292 F.2d 948 (CCPA 1962) for the proposition that "one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment in humans."). In summary, Applicants maintain that they have put forth sufficient evidence demonstrating that the ability of a compound to modulate an immune response in an in vitro representation assay is reasonably correlated with its ability to similarly modulate an immune response in vivo, and 35 U.S.C. 112 requires no more.

Applicants' arguments have been carefully considered, but have not been found persuasive, because although Bellone et al. does not specifically teach *in vitro* presentation

assays, the teachings of Bellone et al. are drawn to the unpredictability of modulating an immune response *in vivo*. Although Applicants are not required to show clinical efficacy, and the Examiner is not requiring such evidence, given that the evidenced provided is not commensurate in scope with the claims, Applicant has not established a nexus between a fragment of α2M or the α2M receptor and inhibition of an immune response in a human based on the data presented in the specification and one of skill in the art would not predict that any fragment of α2M or the α2M receptor would inhibit an immune response given the unpredictability in the . Furthermore Bellone et al. was cited as drawn to the unpredictability of the art as drawn to enablement, not utility. However, although distinct, the issues of enablement and utility are closely related, and Applicant cites the court finding that "proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility." Extending this reasoning to the question of enablement, given that no animals models have shown that a fragment of α2M or the α2M receptor can inhibit an immune response the arguments are not found persuasive in support of enablement.

The arguments have been carefully considered but have not been found persuasive and the rejection is maintained.

Written Description of α2M fragments

17. Applicants argue that the specification provides sufficient description of the genus of α2M fragments by describing twelve representative species and by describing a combination of identifying characteristics of the genus including amino acid sequence structure and functional characteristics that correlate with the sequence structure. For example, the specification provides twelve exemplary α2M fragments, SEQ ID NOS: 8-19, at page 5 1, lines 16-22. The specification also provides the specific portions of a2M that interact with the α2M receptor, namely amino acids 13 14- 145 1, described at page 13, lines 27-29, Fig. 7B, and in the references provided at page 3, line 34 through page 4, line 7, including Salvesent et al., 1992, FEBS Lett. 3 13: 198-202 and Holtet et al., 1994, FEBS Lett. 344:242-246. Finally, the specification teaches that there is an art-recognized correlation between the structure of the a2M receptor-binding domain identified in Figure 7B as amino acids 13 14-1 45 1, and the functional ability of α2M to bind to the α2M receptor. Specifically, at page 4, lines 8-13, the specification

provides that an "[allignment of α2M receptor ligands identifies a conserved domain" which "spans amino acids 1366-1 392 of human α2M and that two of those conserved residues are required for binding to the a2M receptor, as demonstrated by Nielsen et al., 1996, *J.* Biol. Chem. 27 1 : 12909-9 12. Accordingly, appropriate written description is provided for the α2M fragments of claims 3 1 and 7 1. Thus, the specification provides twelve specific examples of the genus of a2M fragments encompassed by the claims. The specification further provides distinguishing attributes of the genus, ***e.g.,*** the specific portion of the α2M protein from which the fragments are derived and an art-recognized correlation between the structure of that portion of the a2M protein and the function of binding to the α 2M receptor. Nevertheless, the Examiner contends that "Applicant's [sic] reliance on general structure (i.e., α2M receptor binding domain) is inadequate because specific not general disclosure is required . . ." Applicants do not understand the Examiner's characterization of the α2M receptor binding domain of α2M as a "general" disclosure, since, as discussed above, the specific portions of α2M that interact with the α2M receptor, namely amino acids 1314-1451 and the conserved region therein of amino acids 1366- 1392, are described in the specification at page 13, lines 27-29, in Fig. 7B, and in the references provided at page 3, line 34 through page 4, line 7, including Salvesent et al., 1992, FEBS Lett. 313:198-202 and Holtet et al., 1994, FEBS Lett. 344:242-246. Accordingly, Applicants maintain that the written description requirement of 35 U.S.C. § 112, first paragraph, is satisfied with respect to the genus of α2M fragments recited in the claims.

Applicants' arguments have been carefully considered, but have not been found persuasive. Although Applicants provide fragments of α2M and the domain of α2M that binds to the α2M receptor, neither the specification nor the art of record describes any fragments of α2M that interfere with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in a human. Although the domain of α2M for binding to the α2M receptor is known in the art, neither the specification nor the art of record describes the sequences of α2M critical for interfering with the interaction of a heat shock protein and inhibiting an immune response in a human, which may or may not be the same as those for of the binding of the α2M receptor.

The arguments have been carefully considered but have not been found persuasive and

the rejection is maintained.

Written Description of α2M receptor fragments

18. Applicants argue that the Examiner contends that the specification does not provide any complete or partial structure of an α2M receptor fragment that interferes with the interaction of a heat shock protein and an α2M receptor. Applicants argue that the Examiner acknowledges that the specification discloses the p80 fragment, which is a fragment of the α2M receptor that interferes with the interaction of a heat shock protein with the a2M receptor in an in vitro re-presentation assay (as demonstrated by Applicants' specification, e.g., at page 71, lines 34-37 to page 73, line 28). Applicants argue that the Examiner nevertheless contends that "this does not provide a description of α2M receptor fragments that interferes [sic] with the interaction of heat shock protein with the α2M receptor and inhibits an immune response in vivo in a human that would satisfy the standard set out in Enzo." Applicants argue that the p80 fragment taught by the specification is the complete structure of an α2M receptor fragment that interferes with the interaction of heat shock protein with the α2M receptor and is reasonably expected to inhibit an immune response in vitro (i.e., an antigen specific T cell response as measured in a re-presentation assay), and Applicants have demonstrated a reasonable correlation between the ability of a compound to inhibit an immune response in an in vitro re-presentation assay and its ability to inhibit an immune response in vivo. In view of this, Applicants fail to understand the grounds for the Examiner's contention that the description of the p80 fragment is insufficient.

Applicants argue that the Examiner contends that the specification does not describe a "representative number" of α2M receptor fragments or "structural features common to the members of the genus" sufficient to satisfy the Lilly standard (see the Office Action at p. 27, para. 2 to p. 28). Applicants addressed this rejection in the Amendment filed June 9, 2005 ("the 2005 Amendment"). Applicants argue that in the 2005 Amendment, Applicants pointed out that the specification provides eight exemplary α2M receptor fragments, namely, three corresponding to SEQ ID NOS: 20-22 (see page 54, lines 15-27, of the specification), four corresponding to SEQ ID NOS: 54-57 (see page 73, lines 13-19, page 13, lines 5-9, and Fig. 3C of the specification), and the p80 a2M receptor fragment. SEQ ID NOS: 20-22 are within the CI

cluster of the α2M receptor, and are fragments of p80. SEQ ID NOS: 54-57 are located between the CI and CII clusters, and are fragments of p80. Applicants argue that the p80 fragment corresponds to an N-terminal fragment of the α2M receptor which includes the CI cluster and additional sequence between the CI and CII clusters (see page 73, lines 13-19, and Figure 8B of the specification). The specification also teaches that the p80 fragment binds to the heat shock protein gp96 (see page 71, line 34 to page 73, lines 1-12, and page 75, lines 1-28, of the specification). Applicants argue that the in view of the evidence of binding between the heat shock protein gp96 and the p80 fragment, a reasonable expectation exists that α2M receptor fragments comprising sequence derived from the p80 fragment will interfere with the interaction of an HSP with the receptor, as specified by the claims. Such fragments are exemplified by p80 itself and the seven additional sequences recited above. Applicants argue that in the 2005 Amendment, Applicants also pointed out that the specification provides distinguishing attributes of the fragments which comprise HSP-binding portions of the α2M receptor, e.g., at page 54, lines 7-15, and in Figure 8B. For example, the specification provides that the HSP-binding portion of the α2M receptor consists of, or comprises, at least one complement repeat or a cluster of complement repeats, preferably CI-II. The specification also provides structural details as to the length of the HSP-binding fragment of the α2M receptor, e.g., that it can consist of at least 10, 20, 30, 40, or most preferably 80 amino acids; or that such fragments are not larger than 40-45 or 80-90 amino acids. Finally, the specification describes a particular embodiment of an α2M receptor fragment, namely an 80 kDa fragment, which binds to the heat shock protein gp96 and is reasonably expected to inhibit the re-presentation of gp96 by antigen presenting cells (see e.g., the specification at page 71, lines 34-37 to page 73, line 28, and the portion of the α2M receptor sequence highlighted in bold in Fig. 8B, corresponding to amino acid residues 327-346, described at page 14, lines 2-3). To summarize, the specification satisfies the Lilly standard by provides eight exemplary α2M receptor fragments as well as a correlation between the α 2M receptor fragments and HSP-binding, provided by the specific example of the p80 fragment. The specification further provides distinguishing attributes of the genus, e.g., the specific portion of the α 2M receptor protein from which the fragments are derived, their preferred length, and an

art-recognized correlation between the structure of that portion of the α2M receptor protein and the ligand-binding function of the α2M receptor.

Applicants' arguments have been carefully considered, but have not been found persuasive. Although the specification provides the p80 fragment of the α2M receptor, various other fragments of the α2M receptor, and appears to prophetically point to the HSP-binding portion of the α2M receptor (which consists of, or comprises, at least one complement repeat or a cluster of complement repeats, preferably CI-II) neither the specification nor the art of record describes any fragments of the α2M receptor that interfere with the interaction of a heat shock protein with the α2M receptor and inhibits an immune response in a human. Although the specification provides the p80 fragments the α2M receptor, for the reasons of record and set forth above in regard to the enablement of the α2M receptor fragment, the specification has not described α2M receptor fragment for interfering with the interaction of a heat shock protein and inhibiting an immune response in a human as no nexus has been established between an α2M receptor fragment and inhibiting an immune response in a human. Even if it were found that the p80 fragment of the α2M receptor were able to interfere with the interaction of a heat shock protein and inhibit an immune response in a human, the example of a single species would not be sufficient to describe the claimed genus of α2M receptor fragments for the reasons set forth on p. 28 of the Office Action of September 21, 2006.

The arguments have been carefully considered but have not been found persuasive and the rejection is maintained.

Sequence Listing

19. The specification is objected to because SEQ ID NO: 4 in Figure 7a, the predicted amino acid sequence of α2M protein does not match SEQ ID NO: 4 in the sequence listing which is a nucleotide sequence. Thus SEQ ID NO: 4 is not a proper identifier of the amino acid sequence in Figure 7a and is an improper disclosure of amino acid sequences without a proper sequence identifier. Hence, the disclosure fails to comply with the requirements of 37 CFR 1.821 through 1.825. In the absence of a sequence identifier for each sequence, Applicant must provide a computer readable form (CRF) copy of the sequence listing, an initial or substitute paper copy of the sequence listing, as well as any amendment directing its entry into the specification, and a

statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e-f) or 1.825(b) or 1.825(d). *Failure to supply the appropriate sequences identification numbers in response to this action will be considered non-responsive.*

20. All other objections and rejections recited in the Office Action of September 21, 2006 are withdrawn.

21. No claims allowed.

22. This action is a **final rejection** and is intended to close the prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an appeal to the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below.

If applicant should desire to appeal any rejection made by the examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims appealed. The Notice of Appeal must be accompanied by the required appeal fee.

If applicant should desire to file an amendment, entry of a proposed amendment after final rejection cannot be made as a matter of right unless it merely cancels claims or complies with a formal requirement made earlier. Amendments touching the merits of the application which otherwise might not be proper may be admitted upon a showing a good and sufficient reasons why they are necessary and why they were not presented earlier.

A reply under 37 CFR 1.113 to a final rejection must include the appeal form, or cancellation of, each rejected claim. The filing of an amendment after final rejection, whether or not it is entered, does not stop the running of the statutory period for reply to the final rejection unless the examiner holds the claims to be in condition for allowance. Accordingly, if a Notice of Appeal has not been filed properly within the period for reply, or any extension of this period obtained under either 37 CFR 1.136(a) or (b), the application will become abandoned.

22. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE

OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0890. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Peter J. Reddig, Ph.D.
Examiner
Art Unit 1642

PJR

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